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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/779,917	02/17/2004	Nancy Allbritton	60021010-0034	8995

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,917	ALLBRITTON ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments filed on March 24, 2005 have been received and entered. Claims 54, 56 and 58 have been amended. Claims 62 and 63 have been added. No claims have been canceled. Accordingly, claims 54-63 are pending and are examined on the merits herewith.

The text of those sections of Title 35, U.S. code, not included in this action can be found in a prior office action.

Oath/Declaration

In view of Applicants' supplemental Application Data Sheet, stating that the instant application is a continuation-in-part of Application Nos. 09/358,504 (now US Patent No. 6,335,201) and 09/036,706 (now US Patent No. 6,156,576) the requirement for a new Oath or Declaration is withdrawn. This amendment to the application clarifies the relationship between it and the prior applications.

Specification

In view of Applicants' amendments to the specification and provision of a Sequence Listing, the objections to the specification have been withdrawn.

Claim Objections

Claim 58 is objected to because of the following informality. The claim recites "detecting the label to distinguishable identify the substrate molecules." Presumably,

distinguishably identifying the substrate molecules is meant. Appropriate correction is requested.

Claim Rejections - 35 USC § 112, first paragraph

Claims 54-61 are again rejected, and claims 62-63 are rejected, under 35 §112, first paragraph, as failing to comply with the written description requirement. This rejection- that the specification did not disclose any substrate molecules for an oncoprotein- was discussed in a prior Office action.

All of Applicants' arguments have been considered, but are not persuasive of error. Applicants assert that the specification provides detailed examples using model substrates and that the details in the specification teach how to make and use the invention. But, as noted previously, the specification does not name any molecules that are substrates for an oncoprotein. Experiments are presented in which the model compounds fluorescently labeled protein kinase C (PKC), fluorescently labeled protein kinase A (PKA) and fluorescently labeled cdc2K (in phosphorylated and unphosphorylated forms for PKC and Fl-scdc2K) are separated and detected, but there is no indication as to which oncoproteins these molecules are substrates of. Applicants note on p. 7 of the specification that more than 120 oncogenes are known, and that many of these are known to be kinases, and that, therefore, the substrates are known. Whether or not this statement is true, the specification must specify at least one oncoprotein substrate molecule, and preferably more, in order to satisfy the written description requirement. Accordingly, the rejection of record is maintained.

Claims 54-61 are again rejected, and claims 62-63 are rejected, under 35 §112, first paragraph, as failing to comply with the enablement requirement. This rejection was discussed in a prior Office action (because the specification did not disclose any substrate molecules for an oncoprotein, and because only one oncoprotein related to one type of cancer was presented, without a substrate, the specification does not teach methods of detecting cancer or testing a compound for anti-cancer activity).

All of Applicants' arguments have been considered, but are not persuasive of error. Applicants assert that the specification provides detailed examples using model substrates and that the details in the specification teach how to make and use the invention.

In reply, the examples show experiments with normal mouse and leukemic rat cells in which fluorescently labeled PKC in both phosphorylated and unphosphorylated forms is detected after the cells are lysed. The cells may be contacted with a compound that enhances phosphorylation (PMA) so that larger amounts of each may be detected (see pp. 25-38). But, there is no indication as to which enzyme catalyzes the phosphorylation reaction. Because the reaction occurs in normal cells, there is no indication that this enzyme is an oncoprotein. An experiment is also presented in which fluorescently labeled PKC and PKA and phosphorylated fluorescently labeled PKC that were present in leukemic rat cells are separated and detected (see Fig. 11). Again, the specification does not teach what the phosphorylating enzyme or kinase is. Additionally, the specification contains an experiment with Xenopus oocytes that contain

fluorescently labeled PKC and cdc2K. Phosphorylated and unphosphorylated forms of each molecule are present. After lysis of the cells, these four molecules may be separated and each detected. Similarly to the other experiments, the specification does not teach what the phosphorylating enzyme or kinase is. Consequently, the specification does not teach any one particular oncoprotein that is an enzyme that phosphorylates a substrate, such as PKC, PKA or cdc2K. If no phosphorylating enzymes that are oncoproteins are disclosed, then their substrates are also not disclosed. Thus, the specification does not teach a method of detecting cancer in which such an oncoprotein enzyme and substrate pair is used. The specification also does not teach any methods of testing a compound for anticancer activity. Therefore, the rejection of record in maintained.

Claims 54-57 are again rejected under 35 §112, first paragraph, as failing to provide an enabling disclosure. This rejection was discussed in a prior Office action (these claims recite a method of detecting cancer comprising measuring the presence of oncogenic activity, but in the specification no link is demonstrated between cells with oncogenic activity and cells with cancer).

All of Applicants' arguments have been considered, but are not persuasive of error. Applicants have provided a definition for oncogene, but in view of the experiments described above, there appears to be no difference in the oncogenic activity of the leukemic cells tested (RBL cells) versus the normal cells tested (NIH/3T3 cells). Thus, the specification does not teach how the claimed method is used to detect

cancer. Applicants note that p53 in its normal form is a tumor suppressor gene and not an oncogene. Only in its mutated form or if excess copies are present does it become an oncogene. Nevertheless, as discussed above, the specification does not identify any oncoprotein/oncoprotein substrate molecule pairs, as recited in the claims, that are linked to cancer and may be used in an assay to detect cancer. Therefore, the rejection of record in maintained.

Claims 62 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, claims 62 and 63 recite that the intracellular chemical reaction is enzyme catalysis by a kinase.

No kinases that function as enzymes, particularly enzymes that are oncoproteins, are disclosed in the specification. As noted above, the specification discloses PKC, PKA and cdc2K. But, in the instant application, these are substrates that may be phosphorylated by unknown and undescribed kinases. There is no evidence that any representative species of such a large and varied genus- kinases that act on oncoprotein substrate molecules- were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any kinases that act on oncoprotein substrate molecules. Therefore, claims 62 and 63 fail to satisfy the written description requirement.

Claims 62 and 63 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As discussed above, these claims recite kinases that act on oncoprotein substrate molecules that are not disclosed in the specification.

As a result, the scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art to determine that cancer may be detected or that anti-cancer compounds may be screened for by a method in which a kinase reacts with labeled oncoprotein substrate molecules. Further, if the identity of the kinase is unknown, it cannot be determined what its substrate would be.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some

experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary (immense, because Applicants assert that cancer may be detected and that anti-cancer drugs may be screened for in methods involving the reaction of a kinase and an oncoprotein substrate molecule without identifying the kinase), (2) the amount or direction or guidance presented (no guidance is presented for identifying the kinases that may be used in the claimed methods), (3) the presence or absence of working examples (none involving a kinase that acts on an oncoprotein substrate molecule is presented), (4) the nature of the invention (detecting cancer and screening for anti-cancer drugs by a method involving the reaction of a kinase and an oncoprotein substrate molecule is not enabled), (5) the state of the prior art (detecting cancer and screening for anti-cancer drugs by a method involving the reaction of a kinase and an oncoprotein substrate molecule, in which the labeled substrate is put into cells, the reaction products are liberated from cells, and the altered and unaltered substrate molecules are separately detected is not known), (6) the relative skill of those in the art (very high, that of highly trained research scientist), (7) the predictability or

unpredictability of the art (see below), and (8) the breadth of the claims (broad, as discussed above).

To demonstrate that cancer may be detected and that anti-cancer drugs may be screened for in methods involving the reaction of a kinase and an oncoprotein substrate molecule, many experiments would have to be conducted under a wide range of conditions. In these experiments, samples from a number of animals with and without cancer (without as controls) would have to be obtained and tested. For each type of animal studied, samples would have to be obtained and tested from subjects having numerous types of cancers. Suitable kinases and oncoprotein substrate molecules would have to be identified. The results of the experiments would have to show that a number of different, specific substrates are each altered by a kinase and that elevated levels of altered substrate correlate with the presence of cancer. In drug screening experiments, decreased levels of altered substrate must correlate with exposure to compounds known to have an anti-cancer effect.

Such experiments and data are missing from the specification. A great deal of guidance is needed to establish cancer detection and drug screening capability because the claims recite detecting any type of cancer, or anti-cancer activity, by measuring the activity of any oncoprotein in an assay with any type of kinase and labeled substrate. Even if detection of one type of cancer, or the ability to screen anti-cancer drugs can be shown in one type of animal, without a very large amount of data, such a result could not be expected with a different type of cancer or anti-cancer activity

in a different animal, especially if a different kinase or a different labeled substrate is used.

Regarding predictability, because the specification does not provide guidance for detecting cancer or screening for anti-cancer drugs with an assay involving the reaction of an oncoprotein substrate and a kinase, it cannot be predicted that any type of cancer can be detected, or that anti-cancer drugs can be screened, by an assay in which a kinase reacts with an oncoprotein substrate to produce unaltered and altered substrate molecules. Accordingly, claims 62-63 fail to satisfy the enablement requirement.

Claim Rejections - 35 USC § 112, second paragraph

Claims 54-61 are again rejected, and claims 62-63 are rejected, under 35 §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. This rejection was discussed in a prior Office action (claims 54 and 58 are incomplete because they recite, respectively, a method of detecting cancer and a method of testing a compound for anti-cancer activity, but the claim recitations end with the step of determining the presence of a chemical reaction and do not relate the result to the preamble).

All of Applicants' arguments have been considered, but are not persuasive of error. Applicants assert that relation back to the preamble is not necessary to render the metes and bounds of the claims clear. But claim 58, for example, a method of testing a compound for anti-cancer activity, recites the steps of exposing cancerous cells to a compound, measuring the presence of oncogenic activity by providing labeled

substrate molecules within the cells, allowing the substrate molecules to take part in a chemical reaction to produce altered substrate molecules, liberating the substrate molecules and the altered substrate molecules from the cells and determining the presence of the chemical reaction from the presence of the altered substrate molecules. This claim is indefinite and incomplete because, as written, there is no relationship between the compound and anything else, i.e., any other steps or molecules. There is no relationship between the compound and oncogenic activity; there is no relationship between oncogenic activity and the chemical reaction. Consequently, there is no relationship between the compound and the chemical reaction.

Similarly, in claim 54, as written, there is no relationship between oncogenic activity and the chemical reaction. The claim recites a method of detecting cancer, comprising the step of measuring the presence of oncogenic activity. But, oncoprotein substrate molecules are provided within cells, and these substrate molecules undergo a chemical reaction. The chemical reaction is not linked to the oncoprotein. Therefore, this method can detect molecules that have undergone a chemical reaction but cannot detect oncogenic activity or cancer.

Thus, the rejection of record is maintained.

Double Patenting- Obviousness-type

Claims 54-61 are again rejected, and claims 62-63 are rejected, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 16 of U.S. Patent No. 6,740,497. This rejection was discussed in a

previous Office action (the cancer detection method of instant claim 54, and the anti-cancer drug screening methods of instant claims 58 and 60, are the method steps of patented claims 1 and 16 for measuring oncogenic activity; patented claim 16 has the extra step that the molecules detected are detected in a quantitative manner).

Applicants' argument has been considered, but it is not persuasive of error. Applicants assert that a double patenting rejection is not proper, because motivation for using the patented method to detect cancer or screen anti-cancer drugs was not provided. In reply, it was stated in the previous Office action that "One of ordinary skill in the art would have recognized that, where the activity of a particular oncogene is known to be related to malignant cancerous cell growth, the method of the parent issued patent would have been applied for the detection of cancer in a cell or cell sample by measuring the activity of that oncogene. Similarly, the method of instant claim 58, with one extra, initial step recites the same method as claim 1 of the issued patent, and claim 60, with one extra, initial step, recites the same method as claim 16 of the issued patent. The initial step in each case is that the cell or cells are exposed to a test compound, and then the presence of oncogenic activity is determined. Claims 58 and 60 are drawn to a method of testing a compound for anti-cancer activity. One of ordinary skill in the art would have recognized that, in screening for a compound with a certain pharmaceutical property, such as the ability to inhibit or enhance a certain chemical reaction, a cell or a sample of cells would have been exposed to the test compound and then used in an assay method that detected whether or not that chemical reaction still occurred (see, e.g., Bissery, US 5,728,687, column 2, lines 40-63,

and column 3, which discloses a method for determining the killing activity on tumor cells of several anti-cancer drugs, in which cells are exposed to the drugs and the degree of cell killing is then determined). Therefore, there is no patentable distinction between instant claims 58-61 and claims 1 and 16 of the issued patent." Thus, clearly, motivation has been provided. To reiterate, where one of ordinary skill in the art recognized that the activity of a particular oncogene was related to cancer, one of ordinary skill in the art would have used a method of determining the activity of that oncogene or oncoprotein to detect cancer. Patented claim 1 or 16 is this method.

Where one of ordinary skill in the art was looking for an anti-cancer drug screening method and recognized that the activity of a particular oncogene was related to cancer, one of ordinary skill in the art would have known to expose cancer cells to a test compound and use a known method of determining the activity of that oncogene or oncoprotein to assess the effects of the test compound. Patented claim 1 or 16 is this method. Therefore, the requirement for a Terminal Disclaimer is maintained.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1651

rk
2005-04-26

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit 1653